

Statistical Methodes Applied in Pharmacotherapy

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SUMMARY

Introduction: Pharmacotherapy dealing with drug research is extremely complex process because in addition to basic knowledge in pharmacology, it includes both knowledge in clinical medicine and medical statistics.

Methods: Statistical methods applied in medical research have been studied on examples of individual statistical methods applied in particular clinical trials.

Topic: The following problems have been discussed: study design, study plan, criteria for selecting patients, the required and sufficient minimum number of patients in the clinical trial, the selection of the most commonly used descriptive and analytical statistical procedures, but also a critical review of analytical statistical procedures that have great potential in checking the conformity of everyday clinical practice with evidence-based medicine.

Conclusions: Knowledge of statistical methods is a valuable companion and tool of clinicians, since it enables them to carry out appropriate research with the best possible conclusions based on medical evidence.

Keywords: statistical methods, evidence-based medicine, clinical medicine, pharmacotherapy

INTRODUCTION

International consensus has not yet been achieved regarding definition of Pharmacology as a science. Biologists define Pharmacology as a biological discipline dealing with the effects of drugs, with wide definition of a drug: any natural or endogenous molecule (outside or inside the body) having biochemical or physiological effect on a cell, tissue, organ or an organism [1]. On the other hand, clinical pharmacologists and pharmacotherapists de-

fine Pharmacology as a science studying four main processes of use of drugs in treatment and/or prevention of diseases [2], which are: (1) pharmaceutical – possibility of drug uptake in the patient's organism, (2) pharmacokinetic – possibility of drug uptake at the place of its action, (3) pharmacodynamics – defining all the effects of a drug, including the main ones, expected, i.e. necessary ones or/and side effects, unwanted either expected or unex-

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pected effects (side effects), and (4) pharmacotherapeutic – consideration of the possibility of translating the pharmacodynamic effects of the drug into the pharmacotherapeutic effects. In addition, American Association of Pharmaceutical Sciences (AAPS) defines Pharmacology as a science studying the action of a drug on a living system [3]. However, AAPS presents medically problematic assumption that clinical science engages in studying the application of drugs in the treatment of diseases. Yet, from the clinical medicine point of view, it is not the illness that is treated but a person affected by the illness, with a whole spectrum of its health characteristics - from demographic (gender, race, age), social (exposure to risk factors during work, habitual habits, etc.), all the way to clinical ones (medical history indicators, clinical signs, symptoms, laboratory indicators, radiological findings), which most often all define a certain diagnosis or diagnoses, the severity of the disease or severity of the pathological condition of the patient.

Also, there is no uniquely established consensus in the definition of the drug. According to the Republic of Serbia Law on Medicines and Medical Devices, [4] the medicinal product is a product that is placed on the market with a certain strength, pharmaceutical form and package, containing a substance or combination of substances that have been shown to have the ability to treat or prevent disease in humans or animals, as well as a substance or combination of substances that can be used or applied to humans or animals, with the intent to re-establish, improve or modify the physiological function by pharmacological, immunological or metabolic action or to establish a medical diagnosis. The Federal Food and Drug Administration (FDA) similarly defines the drug as a product, with the addition that the drug contains the active ingredient in general, but not necessarily, together with inactive ingredients [5]. The term also includes a finished pharmaceutical formulation that does not contain the active ingredient, but is intended for use as a placebo (a pharmaceutical formulation or a product which when applied to a patient creates a conviction that it helps or treats). Of course, according to these definitions, for anything to be considered a drug, a substance must pass the path from the active substance to the pharmaceutical formulation, i.e. from the pharmaceutical formulation to the medicinal product approved for human

and animal application for certain pharmacotherapeutic indications [2].

METHODS

Regarding the application of certain statistical methods in the research that follows the mentioned processes, we will here focus on examples of individual statistical methods in clinical trials.

The selection of a research problem with the consequent setting of the research objectives is almost always related to determining the number of respondents, or the number of observation units. Namely, from the point of view of medical ethics, it is necessary to accurately calculate the smallest number of sample units (“sample size”), either patients or animals that is both needed and sufficient to prove particular medical effect or effects in a precisely defined study sample. In order to determine an adequate sample size in a clinical or preclinical experiment, the first requirement that a medical researcher has to satisfy is the excellent knowledge of the population affected by the disease in general and all of their characteristics in order to define the study sample precisely so as to qualitatively and quantitatively represents this population in the best possible way (for example, the population of patients affected by a particular disease) with inevitable but defined limits and the extent of deviation from the actual population. It is therefore important to point out that medical statistics does not deal with sampling, but rather with assessing the representative sets of precisely defined and pre-selected types of data to be obtained by clinical measurements in the study sample, and relative to the actual population. The entire actual population of the respondents is practically inaccessible to the researcher, but at the same time unnecessary for analysis and conclusions. Hence the question, what references a medical researcher in clinical pharmacology or clinical medicine in general, should use in studying the population of patients with a certain illness, diagnosis or defined health problem? These are certainly good clinical practice guidelines, both international and national. Good clinical practice guidelines synthesize evidence based information from observational studies or review studies, so-called meta-analyzes of epidemiology (incidence and prevalence, risk factors, co-morbidity), etiology and pathogenesis, di-

Observation studies	Experimental studies
A. Descriptive	A. Controlled studies:
B. Analytical:	A1. Parallel or simultaneous controls
B1. Anamnestic (retrospective)	A2. Sequential controls
B2. Cross-section studies (examination, prevalence studies)	A3. External controls
B3. Cohort studies (prospective)	B. Studies without controls
B4. Historical cohort studies	

Table 1. Classification of study plans in quantitative research*

* Taken from Statistics for Researchers in Medical Science [Marinković J, 2011] [13]

agnosis, prevention and treatment of patients with a certain illness, diagnosis, syndrome or other clearly defined health problem.

Evidence-based medicine (EBM), its origin, development and importance tied to the Medical Informatics and Medical Statistics, as well as for the realization of the concept of high-quality, efficient and effective health care. By definition, EBM represents a conscientious, explicit and reasonable use of the best evidence in decision-making about therapy and patient care [6]. This implies that the doctor is aware of the importance and strength of evidence in support of the decision-making process in everyday practice [7]. However, according to the stated clinicians' attitude, in daily clinical practice EBM is applied on average in about 20% of cases, although clinicians declare that EBM should certainly be applied in 80% of cases [8–11].

Accepting EBM concept means decision-making based on the following criteria: (a) there is a basic proof; (b) it is available at the time of making the decision; (c) there are strategies for accepting evidence; (d) the evidence has been adopted and applied in practice; and (e) evaluation has been made in terms of whether the desired health outcome corresponds to the original evidence from the research [12].

The hierarchy of research evidence

follows the methodological approaches validity, i.e. the absence of bias in the interpretation of results and conclusions. It is usually considered that a well-designed randomized controlled clinical experiment is at the top of this scale, while the observational study or opinions of the experts are at its bottom.

For successful EBM today it is important to concentrate on three issues: 1) how to ensure that money invested in research is well invested, so that patients receive the health care that reflects the best available research evidence; 2) whose task is to identify that some of the methods and techniques that are being used for years are actually inappropriate or wrong, and 3) which are obstacles to behavior change, with the purpose to achieve the primary goal, i.e. to apply EBM in everyday practice.

On the other hand, statistics are most often defined as a science dealing with the study of mass phenomena, in order to describe, analyze and generalize conclusions. Conducting clinical studies implies the involvement of researchers of various specialties who are sufficiently aware of the need for medical statistics in research, and a statistician with experience in medical research as a team member [13].

TOPIC

In terms of design, research can be observa-

Measurement scales	Characteristics	Example
Nominal	No direction, notifications about attributes - it is the least accurate	Gender, race, ethnicity, etc.
Ordinal	Indicates the order, does not show the size of the difference, but indicates what is greater or less using the logical rank order	Likert scale for measurements in psychometrics
Interval scale	Scale for measuring numerical data - there is no absolute zero, shows the order, but also the absolute differences	Scales for measuring intelligence
Ratio scale	Scale for measuring numerical data - there is an absolute zero, shows the order, but also both relative and absolute differences	Measurement, blood pressure, body temperature, etc.

Table 2. Measurement scales and their characteristics

Table 3. Review of descriptive statistical methods

Measurement scales	Data distribution	A measure of central tendency	Variability measure
Nominal	Any	Mod	Interval of variation - I= Min-Max.
Ordinal	Any	Median	Interquartile range
	Asymmetrical	Median	Interquartile range
Interval scale	Symmetrical (normal Z or Student t- distribution)	Arithmetic mean	Standard deviation (SD), variance (SD ²), variation coefficient (SD / mean), standard error (SE) - represents the quotient of standard deviation and square root of the number of observation units
	Asymmetric	Median	Interquartile range
Ratio scale	Symmetrical (normal Z or Student t- distribution)	Arithmetic mean	Standard deviation (SD), variance (SD ²), variation coefficient (SD / mean), standard error (SE) - represents the quotient of standard deviation and square root of the number of observation units
	Asymmetric	Median	Interquartile range

tional, where respondents are observed and monitored without researcher’s intervention, and experimental, where the conditions (criteria) for the selection of observation units are defined, and which are under the direct control of the researcher and his intervention (Table 1).

The probability of obtaining useful conclusions is by large influenced by determining the correct sample size. Sample size is a complex function derived from the following parameters: a) variability of data set; b) types of analytical statistical methods; c) accuracy and precision (point or more frequently, interval estimates given for an unknown parameter from the basic statistical set - the required accuracy is usually at a probability level of at least 0.95 and the precision is at a maximum of 20% deviation from the true value), and/or d)

power - in discovering possible differences.

Characteristics of the *data set* are divided into: 1) attributive, nominal, categorical or discrete, and 2) quantitative or numerical, which can be continuous or discontinuous (interrupted). The type of variable is defined by the level of measurement, or type of measurement scale. The measurement scale can be defined as the measurement level or data category. Table 2 presents the classification of the measurement scale with their characteristics. Methods for describing the data in terms of determining the data set representative (measures of central tendency), but also its variation (variability measures), are called descriptive statistical methods. Descriptive statistical methods, classified according to the distribution of data and the measurement scale, are shown in Table 3.

Table 4. General review of inferential statistic and analysis of structural series

Group	Methods	Data type	Type of a model regarding the number of dependant variables
Evaluation of data set parameters	Confidence Intervals	Parametric	Univariate
Evaluation of interconnection	Analysis of the main components, factor analysis, optimal scaling, analysis of correspondence, cluster analysis	Parametric	Multivariate
Evaluation of interdependence (dependency)	Univariate and multivariate such as general linear models (linear regression, ANOVA, ANCOVA, MANOVA, MANCOVA, discriminatory analysis), logistic models (logistic regression, Cox proportional hazard analysis), nonlinear models	Parametric and nonparametric univariate, parametric multivariate, mixed parametric and nonparametric multivariate	Univariate Multivariate
Evaluation of Significance of the Difference	Student t-test for independent samples - the difference between two treatments	Parametric and nonparametric	Univariate Multivariate

Inferential statistics deals with the study of methods of analysis, estimation of one or more data series. There are two basic types of data series, which are: 1) structural series - Table 4 and 2) time series [14,15]. *The first series* is called structural series containing comparative data or cross section data. In structural series, the data obtained in a random sample are mutually independent and the series of these data is defined as data sets arranged by a variable [13,14]. *The second group* of series is called time series representing chronologically arranged data [15]. The time series data are mutually dependent, because their temporal order is taken into account.

The methods of the inferential statistics are classified according to the number of variables into univariate, with only one dependent variable, and multivariate, with the effect of one or more factors on multiple dependent variables monitored simultaneously [13, 14]. This applies to methods of inferential statistics for both structural and time series.

Basically, multivariate analytical methods of structural series are also classified into two groups: methods of interdependence of several features and methods of interconnectedness (dependence) of several features [14].

Methods of interdependence are used

Method	Type of test	For of data set distribution	Number of groups (treatments)	Type of sample (design)	Simultaneous assessment of one or more dependent variables
Student t-test for independent samples	parametric	symmetrical	two	independent	Univariate testing
ANOVA	parametric	symmetrical	more than two	independent	Univariate testing
MANOVA	parametric	symmetrical	more than two	independent	Multivariate testing
Student t-test for paired samples	parametric	symmetrical	two	dependent	Univariate testing
ANOVA for repeated measurements	parametric	symmetrical	more than two	dependent	Univariate testing, two-way testing
Mann-Whitney test	nonparametric	asymmetrical	two	independent	Univariate testing
Kruskal-Wollis test	nonparametric	asymmetrical	more than two	independent	Univariate testing
Wilcoxon signed-rank test for matched samples	nonparametric	asymmetrical	two	dependent	Univariate testing
Freidman test	nonparametric	asymmetrical	more than two	dependent	Univariate testing
Kolmogorov-Smirnov test or Chi-square test	nonparametric (difference in frequency distribution)	asymmetrical	more than two	independent	Univariate testing
Fisher's exact probability test	nonparametric (difference in frequency distribution)	asymmetrical	two	independent	Univariate testing
McNemar's test	nonparametric (difference in frequency distribution)	asymmetrical	two	dependent	Univariate testing
Cochran Q-test	nonparametric (difference in frequency distribution)	asymmetrical	more than two	dependent	Univariate testing

Table 5. The most commonly used methods for testing differences, according to the number of factors (group - treatment), the form of distribution, the independence - dependence of data sets (type of sample), and the simultaneous assessment of one or more features

for data exploration, estimation of data structure, estimation of structural and construction measurement validity, detection of hidden data structure, data reduction, defining linear or nonlinear structure for investigated phenomenology (behavioral variables, behavioral research, fatigue, depression, anxiety, quality of life related to health), and exploring potential collinearity among the predictors. It is important to emphasize that these methods do not test hypotheses, as is the case with analytical methods for assessing interconnectedness, or methods for estimating the significance of the difference. Methods of inferential statistics for structure assessment are extremely important both for construction of measurement instruments in behavioral research, as well as for definition, exploration, and description of unknown phenomenology [9,14,16–18].

On the other hand, analytical methods for testing interconnectedness - Table 5, can be classified into: 1) correlation methods and 2) regression methods [13]. Correlation testing (parametric - Pearson correlation coefficient, and nonparametric - Spearman's correlation coefficient) are methods that test the strength of the connection, while the regression methods test the hypothesis of the shape and strength of the connection. Regression methods can be univariate and multivariate. In a broader sense, there is the whole spectrum of general linear models (linear regression, ANOVA, ANCOVA, MANOVA, MANCOVA, discriminatory analysis), logistic models (logistic regression, Cox proportional hazard analysis) or nonlinear models (survival methods) [13,14]. In regression models, one or more dependent variables are brought into operation with one or more independent variables (the predictor). When the dependent variable is continuous, the methods applied are ANOVA, MANOVA [19,20], ANCOVA, MANCOVA, nonlinear functions, multiple linear regression, survival methods, Cox proportional analysis, while in cases where the dependent variable is categorical, then logistic regression [21–25] or discriminatory analysis are applied, which in the narrower sense also belong to classification techniques.

Methods to test the difference between two or more independent data sets are called methods for testing the significance of the difference [13,14]. These methods are also classified into univariate and multivariate. Univariate methods for testing the significance

of the difference are classified into parametric (for symmetric distribution of data sets) and nonparametric (when data are parametric, but datasets are asymmetric, that is, they do not agree with normal or other symmetric data distributions).

It is also a method for testing of the difference, and may be classified into tests for evaluating the difference between independent sets of data, and the second set of tests used to evaluate the difference between the two data sets in a related sample (block design studies) - Table 5.

As a separate group of non-parametric tests, there are tests for evaluating normality - distribution symmetry, that is, tests that assess the compliance of the empirical data set distribution with a normal distribution. Several tests are available to analyze the normal distribution of data, for example, the Kolmogorov-Smirnov goodness-of-fit test [13,23], Shapiro-Wilk W test [23–28] and the Chi-square test for testing normality of distribution [13,23]. The Kolmogorov-Smirnov test is used to analyze the distribution of continuous, numerical data. The Shapiro-Wilk W test is capable of detecting irregularities in a wide range of statistical distributions. The strength of the Shapiro Wilk W test to detect deviations from normal distribution is greater than other normality tests [28–31]. Chi-square test is excellent for testing whether the data is normally distributed. Its main advantage is that it can be applied to discrete distributions, while the main disadvantage is that it requires a very large sample.

When it comes to methods for estimating the data set parameters, these are methods that determine the accuracy of the assertion that a particular parameter (e.g. arithmetic mean) is within the 95% confidence interval, and that the error (a measure of the uncertainty of such a claim) is less than 5%. Most often, the confidence interval for a data set is expressed at an accuracy level of 95% or 99%, that is, an uncertainty level of less than 5%, or less than 1% [13].

Finally, it is necessary to look at the analytical methods of time series, where the analysis is done on data that are chronologically arranged, and mutually dependent. The characteristics and application of the Box-Jenkins method in medical research (class ARIMA, MARIMA, ARIMAX or MARIMAX modeling) are as follows [15,34]: a) it exam-

ines the shape of the time series; b) examines differences in series between two or more periods; c) simultaneously examines the shape of several time series; d) belongs to causal models, because the causes besides the space have their own time dimension; e) reveals significant out layers and, according to their form, reveals potential new causes; f) it is used to predict events and g) it reveals the connection between time series. Although they are rarely used, these methods have great potential when used in the analysis of the most important quality indicators in hospital health facilities (e.g., causes of the lethality) [32–34].

CONCLUSION

Knowledge in the field of medical statistics and correct application of appropriate statistical methods in pharmacological research is a prerequisite for researchers when analyzing other studies during the generation of the idea and preparation of new research, data processing, and statistical measurements, and also after completion of the research as a valuable the individual experience that enhances researcher's intuition in generating new research questions. Knowledge of statistical methods is a valuable companion and tool, especially for clinical researchers, because it allows carrying out research and making the best possible conclusions based on medical evidence in all situations important for everyday clinical work. This is especially important in cases of medical controversy related to the assessment of medical outcomes during the daily use of drugs in all clinically relevant patient populations.

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CONFLICT OF INTEREST

The authors have no conflicts of interest that are directly relevant to the content of this study.

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Statističke metode u farmakoterapiji

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KRATAK SADRŽAJ

Uvod: Farmakoterapijski proces je izuzetno kompleksan proces u istraživanju leka, zato što uključuje bazična farmakološka znanja, ali i znanja u oblasti kliničke medicine i medicinske statistike.

Metodologija: U ovom radu, proučavani su statistički metodi u medicinskim istraživanjima fokusirano na primere primene pojedinih statističkih metoda sa primenom u kliničkim medicinskim istraživanjima.

Tema: Razmatrani su sledeći problemi u pogledu: dizajna istraživanja, plana istraživanja, kriterijuma za izbor pacijenata, potrebnog i dovoljnog najmanjeg broja pacijenata u kliničkom istraživanju, izbora najčešće primenjivanih deskriptivnih i analitičkih statističkih procedura, ali je dat i kritički osvrt na analitičke statističke procedure koje imaju veliki potencijal u proveri usklađenosti svakodnevne kliničke prakse sa medicinom zasnovanom na dokazu.

Zaključak: Poznavanje statističkih metoda dragocen je pratilac i oruđe, kliničara, jer im omogućava da sprovedu prikladno istraživanje uz izvođenje najboljih mogućih zaključaka zasnovanih na medicinskom dokazu.

Ključne reči: statistički metodi, medicina zasnovana na dokazima, klinička medicina, farmakoterapija

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